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Genetically Susceptible Subgroups

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In establishing "safe" standards for all with respect to environmental carcinogenesis, one must consider the heterogeneity of man. Although cancer is considered primarily an environmental disease, there is a wide range of genetic–environmental interaction which ultimately influences the development of malignant disease.

Considerations of subgroups susceptible to environmental carcinogenesis requires consideration of mechanisms of carcinogenesis. It appears that most carcinogens are mutagens, and that carcinogenesis may be viewed as a multistage process.

If mutation is an essential step in the carcinogenic pathway and more than one step is required, then susceptibility to malignancy following mutagen exposure may be affected either by variation in the probability of mutation or variation in the number of necessary mutagenic events. In addition, the probability of malignancy following a mutational event may be influenced by variation in promotional factors acting at each step.

Many different disorders may affect the frequency of mutational events within specific tissues. Tissue specific aberrations in growth control due to an intrinsic increased mutation rate, excessive promotional or growth stimulating factors (neurofibromatosis?), or chronic stimulation due to failure of feedback control mechanisms (immune deficiency syndromes?) may lead to tissue specific increased mutation rates, or increased cell proliferation and thus increased numbers of cells at risk. Exposure of tissues with a high mutation rate to mutagens increases the probability not only of the first mutation, but also of subsequent mutations leading to malignancy.

Disorders characterized by chromosomal instability or increased mutagenesis *in vivo* or *in vitro* may be predisposed to malignancy. This instability may be enhanced *in vivo* or *in vitro* by exposure to specific mutagens. The prototype for such disorders is xeroderma pigmentosum, in which there is clear correlation between clinical susceptibility to carcinogenesis in areas exposed to ultraviolet light and *in vitro* inability to repair ultraviolet-induced DNA damage.

Disorders of chromosomal instability are each unique with specific patterns of chromosomal breakage, *in vitro* mutagenesis, and predisposition to malignancy. In Fanconi's anemia, there is primary bone marrow failure, increased chromosomal breakage *in vivo* and *in vitro*, increased sensitivity to certain mutagens *in vitro*, and a predisposition to leukemia; also there may be a predisposition to hepatoma, enhanced by androgen therapy or transfusion-induced cirrhosis, and a predisposition to squamous cell carcinoma. In Bloom's syndrome there is an immune deficiency, increased sensitivity to mutagenesis *in vitro* as evidenced by increased sister chromatid exchanges, and an increased incidence of leukemia and of other tumors including squamous cell carcinoma and cancer of the colon at an early age. In ataxia telangiectasia there are defects in the immune system, *in vivo* and *in vitro* sensitivity to ionizing radiation, and an increased incidence of leukemia, lymphoma, ovarian and gastric carcinoma. There is a tendency toward chromosomal rearrangement specifically affecting the number 14 chromosome including *in vivo* clonal proliferation which may evolve to malignancy.

Chromosomal instability may provide a marker for cells with increased mutation rates. In addition to the autosomal recessive disorders described above, aneuploidy, as in Down's syndrome, may increase susceptibility to certain mutagens *in vitro*, and may predispose to leukemia. Certain "cancer-prone" families demonstrate chromosomal instability as well.

There may be a genetically determined increased risk of mutation (and cancer) following exposure to

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certain environmental agents due to genetically determined metabolism of that given agent. The brilliant work of Ames and co-workers has demonstrated that ultimate or active carcinogens are in general mutagens, but that many chemicals with *in vivo* carcinogenic properties must be metabolized *in vivo* to their active form. In at least one such system, the aryl hydrocarbon hydroxylase system involved in metabolism of polycyclic hydrocarbons, genetic variation has been reported. Inducibility of the enzyme system has been associated with increased risk of lung cancer in smokers. Although these data have not been confirmed, this system may serve as a model whereby the risk of cancer following exposure to an environmental agent may be modified according to the genetically determined metabolism of that agent.

If malignancy is indeed the result of sequential mutations, one or more of which may be inherited, then there may be a population who is susceptible to mutagenesis not because of any increased probability that they will sustain a mutation, but because they already carry one tissue-specific cancer-predisposing mutation in all cells, and a subsequent mutation may thus greatly increase the probability of malignancy in that tissue.

Recent observations on the effects of a known mutagen/carcinogen, radiation, on patients with hereditary retinoblastoma and the nevoid basal cell carcinoma syndrome demonstrate that individuals with such a hereditary predisposition to malignancy must be considered a unique subgroup with respect to susceptibility to environmental mutagenesis. In each case it was suggested that radiation increased the probability of the specific tumor to which the patients were genetically predisposed, and that the radiation-induced tumors developed within a uniquely short period of time. The short latent period for radiation-induced sarcoma following retinoblastoma, and for radiation-induced basal cell carcinoma following medulloblastoma in patients with the nevoid basal cell carcinoma syndrome were not characteristic of radiation-induced tumors in general, in children, nor were they biologic characteristics of radiation-induced sarcomas or basal cell carcinomas. Indeed these data suggested that radiation provided the second mutational step necessary for carcinogenesis in those individuals who had inherited the first step.

Given a sequential mutational model for cancer, susceptible subgroups might include all individuals who have sustained a primary mutation through a germinal or somatic cell. Individuals who inherit the predisposing mutation are at greatest risk because each cell of the sensitive tissue(s) carries the mutant gene, and a subsequent mutation in any cell may lead to malignancy. However, this model as well accounts for the synergistic, multiplicative effects of mutagens on the risk of cancer in general. Persons who have been exposed to radiation or other mutagens may be much more susceptible to subsequent mutagens due to their previous acquisition of a cancer predisposing mutation.

In those individuals who acquire the first mutation in a somatic cell, promotional factors may be critical in the probability of cancer. Any factor, endogenous or exogenous, including growth stimulating factors, hormones, drugs, depressed immune system, etc., which might give the mutant cell an advantage may increase the probability of malignancy. Immune deficiency syndromes may be viewed in the classical manner as a breakdown in immunosurveillance producing a general promotional effect through failure to recognize or eliminate the mutant cell, or as representing a tissue specific defect in growth regulation of the lymphoreticular system.

Study of subgroups genetically susceptible to carcinogenesis and definition of the mechanism of their susceptibility is critical to any attempt to extrapolate data from animal to man or from high dose to low dose responses. Even if carcinogenesis can be reduced to a simple multistep mutational model, man is not homogeneous with respect to mutation rates, elimination of mutant cells, growth control, metabolism of potential mutagens, or the number of mutational steps necessary for malignancy. Study of each uniquely susceptible subgroup may contribute to our understanding of carcinogenesis in general, and may provide complementary *in vitro* systems for the evaluation of potential carcinogens.

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